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(54) Title: METHOD AND DEVICE FOR DETERMINING THE CONCENTRATION OF A SUBSTANCE IN BODY LIQUID
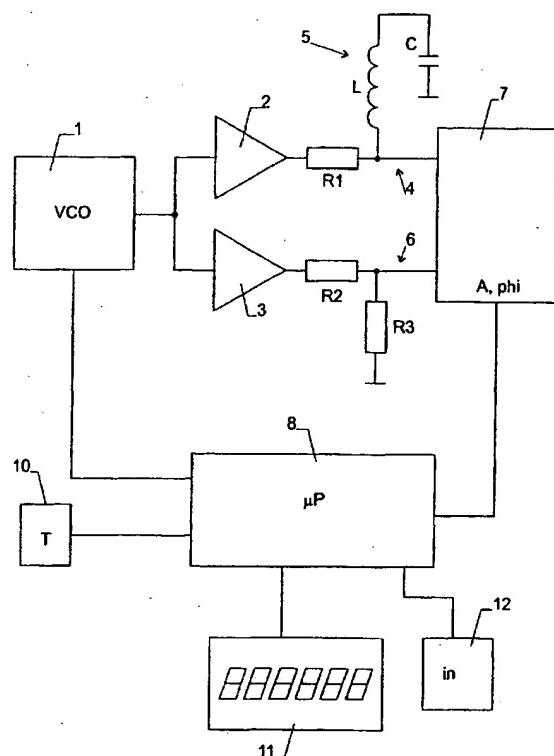
(57) **Abstract:** For measuring the concentration of a substance in body fluid, such as the glucose level in blood or tissue, a strip electrode (18) and a ring electrode (19) are arranged at the specimen. The ring electrode (19) is in direct electrical contact with the specimen while the strip electrode (18) is electrically insulated therefrom. The strip electrode (18) is arranged parallel to an arm or a leg for obtaining a large interaction length. The electrodes (18, 19) form a capacitor in a resonant circuit. A modulated voltage in the MHz range close to or at the resonance frequency is applied to the electrodes and the response of the body fluid is measured. This design allows a measurement of high accuracy.

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Method and device for determining the concentration of a substance in body liquid

Technical Field

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The invention relates to a method and a de-
vice for determining the concentration of a substance in
an in-vitro or in-vivo specimen containing body liquid
according to the preamble of the independent claims.

10

Background Art

Radio wave spectroscopy has been known to
provide promising potential in the in-vitro and in-vivo
15
determination of the concentration of glucose and other
substances in body fluids. In particular, this technology
is of substantial interest for the determination of glu-
cose concentration in blood and/or inter- or intracellu-
lar liquid. A device for measuring blood level glucose is
20
disclosed in US 5 792 668, where two electrodes are
brought into direct contact with the human body and the
impedance is measured between them.

Despite its potential, the technology has not
yet been used in commercial devices, which is attributed
25
to the limited accuracy of the presently known solutions.

Disclosure of the Invention

30

Hence, it is the goal of the invention to
provide a method and device that allow to increase the
reliability of this type of measurement.

This goal is reached by the independent
35
claims.

In a first aspect of the invention, the first
electrode is electrically insulated from the specimen.

Hence, the measured parameter does not depend on the surface conditions of the specimen. Rather, the signal is capacitively coupled to the specimen and the measured parameter depends therefore primarily on the conditions

5 within the specimen. The parameter measured in this way can then be converted to the desired concentration, e.g. by using calibration data.

Preferably, at least two electrodes are provided, wherein the modulated voltage is applied between

10 them. By using two electrodes, a defined field can be established within the specimen. For best signals, it has been found advantageous to place the second electrode in electric contact with the specimen.

The measured parameter preferably depends on

15 the electrical impedance at the electrode(s). It has been found that the concentration of various substances, in particular glucose, affects the real or imaginary part of this impedance because it changes the loss and/or dielectric constant of body fluid.

20 Preferably, the electrode forms part of a resonant circuit, which is operated at or close to its resonance frequency. Under such conditions, a change of the dielectric or loss properties of the specimen leads to substantial shifts in the parameters of the resonant

25 circuit and can therefore be measured with high sensitivity.

A further aspect of the invention is directed to a device particularly suited for in-vivo measurements of the human body. This device comprises an elongate

30 electrode having a width much smaller than its length. A holder is provided to mount the electrode to an arm or a leg with the longitudinal axis of the electrode extending parallel thereto. In this way, a large interaction space is established, which allows to measure the desired con-

35 centration with a higher level of accuracy.

The method and device of the present inven-
tion has been found to be especially suited for measuring
the glucose concentration in body fluid.

5

Brief Description of the Drawings

The invention will be better understood and
objects other than those set forth above will become ap-
10 parent when consideration is given to the following de-
tailed description thereof. Such description makes refer-
ence to the annexed drawings, wherein:
Fig. 1 is a block circuit diagram of a pre-
ferred device for carrying out the invention,
15   Fig. 2 is a view onto a possible embodiment
of the device,
Fig. 3 is a section along line III-III of
Fig. 2,
Fig. 4 is the device of Fig. 3 with a wrist-
20 band,
Fig. 5 shows the behavior of the relative am-
plitude A as a function of frequency,
Fig. 6 is a second embodiment of the circuit,
Fig. 7 is an alternative electrode geometry,
25   Fig. 8 shows measurements at varying glucose
concentrations (mmol/liter) in physiologic solution and
Fig. 9 a third embodiment of the circuit.

30   Modes for Carrying Out the Invention

Fig. 1 shows a block circuit diagram of a
preferred device for carrying out the invention. It com-
prises a voltage controlled oscillator (VCO) 1 as a sig-
35 nal source for generating a sine wave signal. This signal
is fed to two amplifiers 2, 3. The output of first ampli-
fier 2 is connected via a resistor R1 to a first signal

path 4. A resonant circuit 5 comprising an inductance L
and a capacitor C in series is connected between first
signal path 4 and ground. The output of second amplifier
3 is connected via a resistor R2 to a second signal path
6. Second signal path 6 is substantially identical to
first signal path 4 but comprises a resistor R3 as a ref-
erence load instead of resonant circuit 5.

Both signal paths 4, 6 are fed to a measuring
circuit 7, which determines the relative amplitude A of
both signals as well as, optionally, their mutual phase
shift phi. Relative amplitude A can e.g. be the amplitude
of first signal path 4 in units of the amplitude of sec-
ond signal path 6 (wherein the amplitudes are the peak
values of the sine waves).

The output signal of measuring circuit 7 is
fed to a microprocessor 8, which also controls the opera-
tion of VCO 1.

As can be seen from Fig. 1, the device in the
present embodiment further comprises a temperature sensor
10, a display 11 and an input device 12 with user operat-
able controls, all of which are controlled by microproc-
essor 8.

Inductance L of the device of Fig. 1 can be
generated by a coil and/or by the leads and electrodes of
capacitor C. Its value is generally known with reasonable
accuracy.

Capacitor C of the device of Fig. 1 is used
as an antenna for probing a specimen. For this purpose,
it is formed by electrodes that are arranged near the
specimen. The geometry of the electrodes is selected such
that the electric field generated by them extends into
the specimen and the body liquid to be measured. Suitable
geometries are discussed below. As mentioned above, at
least one of the electrodes of the capacitor is electri-
cally isolated such that capacitor C is primarily a ca-
pacitive load, the capacitance and loss of which depends

on the electrical properties (i.e. the response) of the
specimen at the frequency of VCO 1.

To measure the concentration of a substance
in the body fluid of the specimen, microprocessor 8 can
5   e.g. initiate a measurement cycle consisting of a fre-
quency sweep of VCO 1. The sweep should start at a fre-
quency fmin below the expected resonance frequency f0 of
the resonant circuit 5 and extend to a frequency fmax
above resonance frequency f. During this sweep, the elec-
10 trical properties of signal path 4 will change substan-
tially, while those of signal path 6 will vary only
slightly. The amplitude determined by measuring circuit A
will therefore fall to a minimum A0 at f0, as shown in
Fig. 5. At the same time, phase shift phi crosses zero.
15   As can be shown, the dependence of A0 on the
dielectric constant $\varepsilon(f)$ and, in particular, on the loss
or conductance $\rho(f)$ of the fluid in the specimen is
stronger than at off-resonance frequencies, which allows
a sensitive measurement of the liquid's response to the
20 electric field.

This is shown in Fig. 8, which represents
measurements of the type shown in Fig. 5 at glucose con-
centrations between 0 and 17.5 mmol/l. The vertical axis
represents the ratio in dB of the signals from first sig-
25 nal path 4 and second signal path 6. The resonance fre-
quency is around 35.5 MHz.

It is presently believed that the specific
impedance of the body fluid, i.e. the specific conductiv-
ity $\rho(f)$ and the dielectric constant $\varepsilon(f)$ in a frequency
30 range between 10 MHz and 2000 MHz, and in particular be-
tween 20 MHz and 70 MHz, are a function of the properties
and concentration of the salty (ionic) components of the
human body. These salty components primarily include sol-
vated sodium, potassium, calcium and other minor ions and
35 their counter ions, the primary counter ion being chlo-
ride. Other non-ionic solvated substances, in particular
substances having a similar range of size as the ion com-

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plexes, can have an impact on the impedance pattern of
the salty body fluid components, provided these sub-
stances occur in sufficient concentration. In particular,
glucose has a similar range of size and is present in
concentrations giving rise to a well detectable variation
of the amplitude A0 at resonance frequency.

In a simple embodiment, only amplitude A0 is
measured as a parameter for the determination of the con-
centration. Suitable calibration data stored in micro-
processor 8 is used to convert amplitude A0 into the de-
sired concentration level.

The effects exploited for the measurement are
temperature dependent. In order to obtain high accuracy
over a wide temperature range, temperature sensor 10 is
brought into thermal contact with the specimen to be
measured. The signals from temperature sensor 10 are used
to correct the obtained result, again using calibration
data obtain from calibration measurements.

A proper design of the electrodes of capaci-
tor C allows to optimize the accuracy and sensitivity of
the present device in a given application. A preferred
geometry of the device for in-vivo measurements in a liv-
ing body is shown in Figs. 2 and 3.

The device comprises a housing 13 closed on
one side by an electrode plate 14. The display 11 is ar-
ranged opposite electrode plate 14. The electronic cir-
cuits 16 are arranged between electrode plate 14 and dis-
play 11.

Electrode plate 14 comprises an electrically
insulating substrate 17 with a strip electrode 18 and a
top or ring electrode 19 arranged on an outer side 20
thereof. An inner side 21 of insulating substrate 17 is
covered by a bottom electrode 22. A plurality of though-
contacts 23 are provided to connect ring electrode 19 to
bottom electrode 22. A further through-contact 24 con-
nects one end of strip electrode 18 to a small bond pad

25 arranged in an opening 26 of bottom electrode 22 on
inner side 21.

Temperature sensor 10 is mounted to bottom
electrode 22. The large number of through-contacts 23 en-
5   sure that bottom electrode 22 follows the temperature of
ring electrode 18 and therefore the temperature of the
specimen closely.

A typical size of electrode plate 14 is 32 mm
x 21 mm. Bottom electrode 22 covers all of inner side 21
10 except for the small opening 26 and is therefore much
larger than strip electrode 18.

Leads 28 are provided to connect bottom elec-
trode 22, contact pad 26 and temperature sensor 10 to the
electronic circuits 16.

15   While bottom electrode 22 and ring electrode
19 are connected to ground, strip electrode 18 is con-
nected to inductance L of resonant circuit 5. Therefore,
the capacitor C is formed between strip electrode 18 as a
first electrode and ring electrode 19 and bottom elec-
20 trode 22 as a second electrode. In other words, the sec-
ond electrode consists of two electrode layers: a top
electrode layer formed by ring electrode 19 and a bottom
electrode layer formed by bottom electrode 22.

An electrically insulating cover layer 29
25 covers all of strip electrode 18 but not ring electrode
19. In other words, strip electrode 18 is arranged be-
tween substrate 17 and cover layer 29. Cover layer 29 is
preferably of a hard, moisture- and salt-impervious mate-
rial such as glass, ceramics, a polycarbonate or diamond-
30 like carbon (DLC) of a thickness preferably between 50
and 100 μm.

As can be seen in Fig. 4, a holder or wrist-
band 31 is attached to housing 13 for fixing the device
to an arm or a leg of a human body with cover layer 29
35 facing the body and a longitudinal axis of strip elec-
trode 18 parallel to the arm or leg. In this way, ring
electrode 19 comes into contact with the user's skin and

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sets the same to ground reference potential. The electric
field generated by strip electrode 18 extends into the
body tissue. Since strip electrode 18 is elongate and has
a width much smaller than its length and extends along
5   the arm or leg, a comparatively large region of the body
is reached by the field. This allows to obtain more sen-
sitive and accurate measurements.

As described above, a pure sine voltage has
been found to be sufficient for obtaining accurate meas-
10 urements. However, other types for modulated voltages,
such as square-wave voltages or pulses can be used as
well. In this case, measuring circuit 7 is preferably
provided with suitable filters for selectively sampling
one or more frequency components. At least one measured
15 frequency component is preferably close to the resonance
frequency of resonant circuit 5 for exploiting the cir-
cuit's high sensitivity to the specimen's properties at
that frequency.

The electrode geometry can be varied for
20 adapting it to a given application. While the design of
Fig. 2 is optimized for a measurement on an arm or leg, a
circular design can be used for measurement on a flatter
body part or an in-vitro sample.

Ring electrode 19 does not necessarily have
25 to form a closed ring as long as it provides sufficient
grounding of the body part to be measured. It can e.g.
also have U-shape or consist of two stripes parallel to
and laterally enclosing strip electrode 18. Ring elec-
trode 19 can also be omitted completely or be covered by
30 cover layer 29, in particular for in-vitro measurements
where noise is low.

Part of a further embodiment of the circuit
is shown in Fig. 6. Here, no direct connection between
resonant circuit 5 and measuring circuit 7 is used.
35 Rather, an antenna electrode 33 is located in proximity
to the electrodes of capacitor C, and measuring circuit 7
measures the signal returned by antenna electrode 33.

A possible arrangement of the electrodes is shown in Fig. 7. As can be seen, antenna electrode 33 is strip shaped and arranged in parallel to strip electrode 18. Both, antenna electrode 33 and strip electrode 18 are

5 covered by cover layer 29 and therefore electrically in-sulated from the specimen.

The device of Figs. 6 and 7 is again sweeping VCO 1 between a frequency fmin below the resonance fre-quency f0 of resonant circuit 5 and a frequency fmax

10 above it. In contrast to Fig. 5, measuring circuit 7 now detects a maximum amplitude A0 at f0, wherein the value of A0 depends on the response, i.e. the electrical prop-erties of the specimen at the resonance frequency f0. The parameter A0 can now again be processed using calibration

15 data as described above.

A comparison of the device of Figs. 1 and 2 with the device of Figs. 6 and 7 shows that the first em-bodiment measures the response of the specimen from the signal reflected to strip electrode 18. The second em-

20 bodiment measures the response of the specimen from the signal transmitted from strip electrode 18 to antenna electrode 33.

It is found that the transmission and reflec-tion show different dependencies on the concentrations of

25 various compounds of the body fluid. Hence, a combined measurement of reflection and transmission allows a fur-ther refinement of the measurement by elimination of the influence of compounds not of interest for the quantity to be measured.

30 A third embodiment of a circuit is shown in Fig. 9. Here, the capacitor C formed by the electrodes is part of the resonant tank circuit of an active, self-oscillating oscillator 40. The amplitude A and frequency f0 of the output signal of oscillator 40 depend on the

35 capacitance and losses in capacitor C. The corresponding signal is fed to measuring circuit 7, which evaluates the parameters A and f0. Measuring the corresponding parame-

ters A and f0 again allows a sensitive measurement of the
desired concentration using calibration data.

     In the examples shown so far, the invention
was used in a device for qualitatively or quantitatively
5 displaying the concentration a substance (such as glu-
cose) in body liquid. The invention can, however, e.g.
also be used in devices that automatically administer
medication to a body, such as an insulin pump, where the
amount and/or time for administering the medication de-
10 pends on the measured concentration. It can also be used
in any other type of device that requires the measurement
of the concentration of a substance in body fluid.

     While there are shown and described presently
preferred embodiments of the invention, it is to be dis-
15 tinctly understood that the invention is not limited
thereto but may be otherwise variously embodied and prac-
ticed within the scope of the following claims.

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Claims

1. A method for determining the concentration of a substance in a in-vitro or in-vivo specimen containing body liquid comprising the steps of

arranging a first electrode (18) at said specimen, wherein said first electrode is electrically insulated from the specimen,

applying a modulated electrical voltage to the first electrode for generating a modulated field in the specimen and

measuring at least one parameter (A, phi) depending on a response of the specimen to the field and determining the concentration therefrom.

2. The method of claim 1 comprising the step of arranging a second electrode (19, 22) at said specimen, wherein the modulated electrical voltage is applied between the first and the second electrode (19, 22).

3. The method of claim 2 wherein the second electrode (19, 22) is in electric contact with the body liquid in the specimen.

4. The method of one of the preceding claims further comprising the step of measuring a temperature (T) of the specimen and using the temperature in the determination of the concentration.

5. The method of one of the preceding claims wherein the modulated electrical voltage is a sine voltage.

6. The method of one of the preceding claims wherein the modulated electrical voltage has a frequency between 10 MHz and 2 GHz, in particular between 20 MHz and 70 MHz.

7. The method of one of the preceding claims wherein the parameter (A, phi, f0) depends on the electrical impedance at the first electrode.

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8. The method of one of the preceding claims wherein the response of the specimen is measured by measuring a signal reflected from the first electrode.

9. The method of one of the preceding claims wherein an antenna electrode (33) is arranged at the specimen in proximity to the first electrode (18) and wherein the response of the specimen is measured by measuring a signal transmitted from the first electrode (18) to the antenna electrode (33).

10. The method of one of the preceding claims wherein the substance is glucose.

11. The method of one of the preceding claims wherein the specimen is a living body.

12. The method of one of the preceding claims comprising the step of using calibration data to convert the parameter (A, phi, f0) to the concentration.

13. The method of one of the preceding claims wherein the first electrode forms part of a resonant circuit (5) having a resonance frequency (f0) and wherein the resonant circuit (5) is operated substantially at the resonance frequency.

14. The method of claim 13 wherein the resonant circuit is at least part of a tank circuit of an active oscillator (40) and wherein the parameter is an amplitude (A) and/or a frequency (f0) of a signal generated by said oscillator (40).

15. The method of claim 13 wherein the modulated voltage is frequency sweeped from a frequency (fmin) below the resonance frequency (f0) to a frequency (fmax) above the resonance frequency, and in particular wherein the parameter is a signal reflected to the first electrode (18) or transmitted to an antenna electrode (33) at the resonance frequency (f0).

16. A device for determining the concentration of a substance in a in-vitro or in-vivo specimen containing body liquid, in particular for carrying out the method of one of the preceding claims, comprising

a first electrode (18) covered by a cover
layer (29) of insulating material,

a signal source (1) connected to the first
electrode (18) applying a modulated electrical voltage to
5   the first electrode (18) for generating an electric field
in the specimen,

a measuring circuit (7) for measuring at
least one parameter depending on a response of the speci-
men to the field, and
10   a data processor (8) determining the concen-
tration from the parameter.

17. The device of claim 16 comprising a
holder (31) for fixing the first electrode (18) to a part
of a body with the cover layer (29) facing the body.

15   18. The device of one of the claims 16 or 17
further comprising an electrically insulating substrate
(17), wherein the first electrode (18) is arranged on a
first side (20) of the substrate (17) between the sub-
strate (17) and the cover layer (29).

20   19. The device of claim 18 further comprising
a second electrode (19, 22) arranged on the substrate,
wherein the signal source (2) is connected to apply the
modulated electrical voltage between the first (18) and
the second (19, 22) electrode.

25   20. The device of claim 19, wherein the sec-
ond electrode (19, 22) comprises a bottom electrode layer
(22) arranged on a second side (21) of the substrate
(17), said bottom electrode layer (22) having a larger
extension than said top electrode layer (18).

30   21. The device of one of the claims 19 or 20,
wherein the second electrode (19, 22) comprises a top
electrode layer (19) arranged on the first side (20) of
the substrate (17), said top electrode layer (19) being
arranged around at least part, in particular substan-
35   tially all, of the first electrode (18).

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22. The device of one of the claims 16 to 21,
wherein the first electrode (18) is elongate having a
width much smaller than a length.

23. The device of one of the claims 16 to 22
5   comprising a first (4) and a second (6) signal path be-
tween the signal source (1) and the measuring circuit
(7), wherein the first electrode (18) in arranged in the
first signal path (4) and a reference load (R3) is ar-
ranged in the second signal path (6), and wherein the
10   measuring circuit (7) is adapted to measure a relative
amplitude (A) and/or phase (phi) of signals from the
first and second paths.

24. The device of one of the claims 16 to 23
wherein the first electrode (18) is part of a capacitor
15   (C) of a resonant circuit (5) comprising the capacitor
(C) and an inductance (L) connected to the signal source
(1).

25. The device of claim 24 wherein the ca-
pacitor (C) and the inductance (L) are arranged in se-
20   ries.

26. The device of one of the claims 24 or 25
wherein the measuring circuit (7) is adapted to measure a
voltage over the resonant circuit (5).

27. The device of one of the claims 24 to 26
25   further comprising an antenna electrode (33) arranged in
proximity to the first electrode (18), wherein the meas-
uring circuit (7) is adapted to measure a signal trans-
mitted from the first electrode (18) to the antenna elec-
trode (33).

30   28. A device for determining the concentra-
tion of a substance in body liquid of a human body, in
particular of one of the claims 15 to 26, comprising
an elongate first electrode (18) having a
width much smaller than a length,
35   a holder (31) for fixing the first electrode
(18) to an arm or leg of a body with a longitudinal axis

of the first electrode being substantially parallel to
the arm or leg

      a signal source connected to the first elec-
trode applying a modulated electrical voltage to the
5 first electrode (18) for generating a modulated field in
the specimen,

      a measuring circuit (7) for measuring at
least one parameter (A, phi, f0) depending on a response
of the specimen to the field, and

10   a data processor determining the concentra-
tion from the parameter.
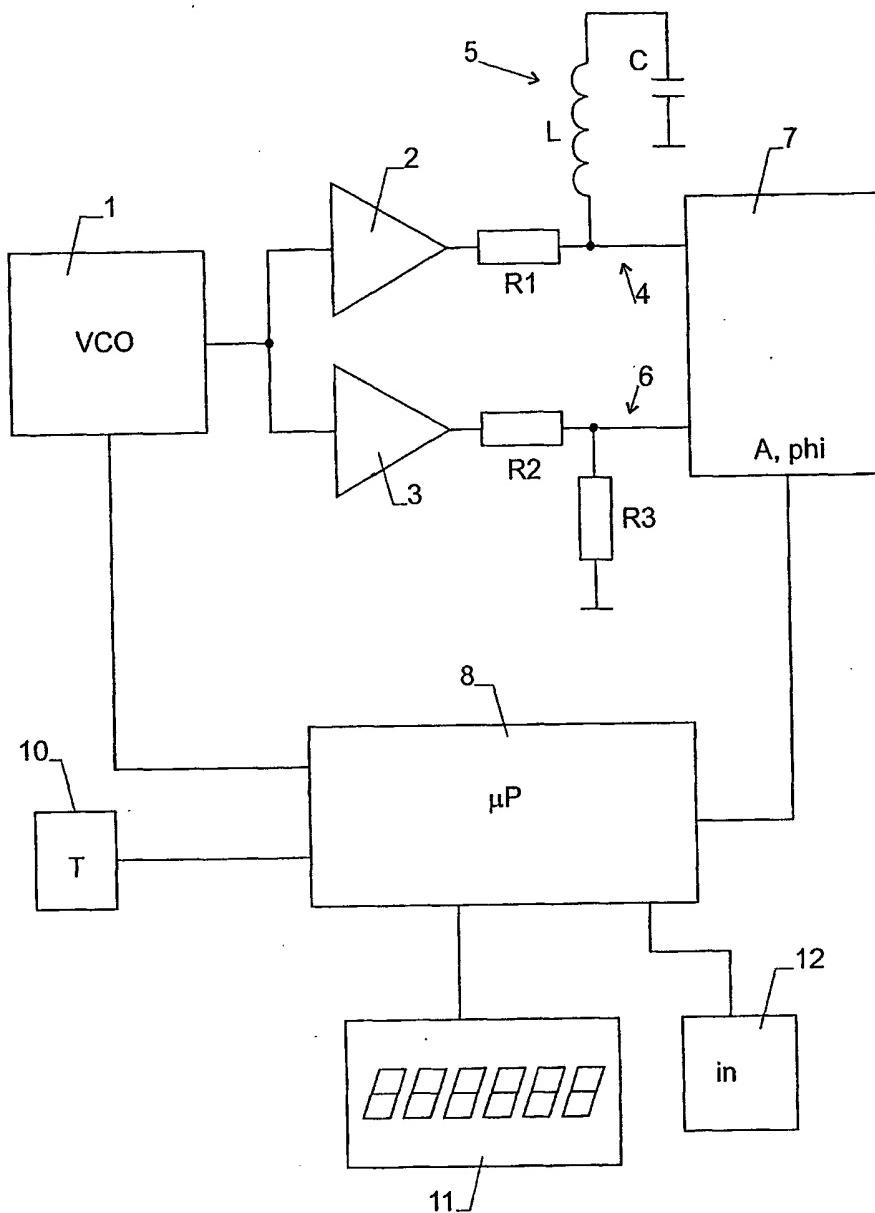
Fig. 1
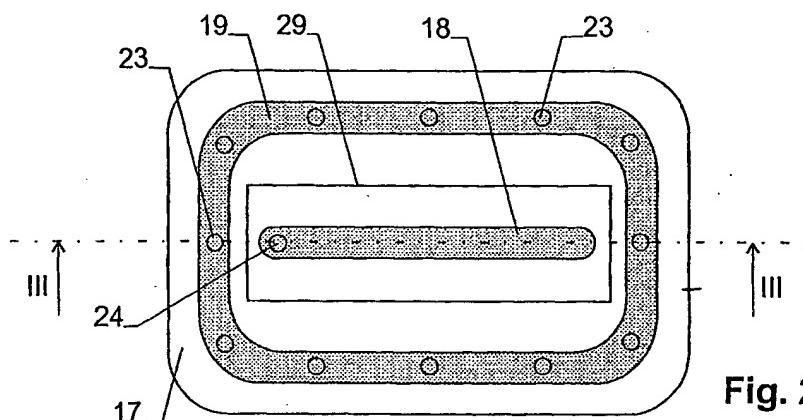
Fig. 2
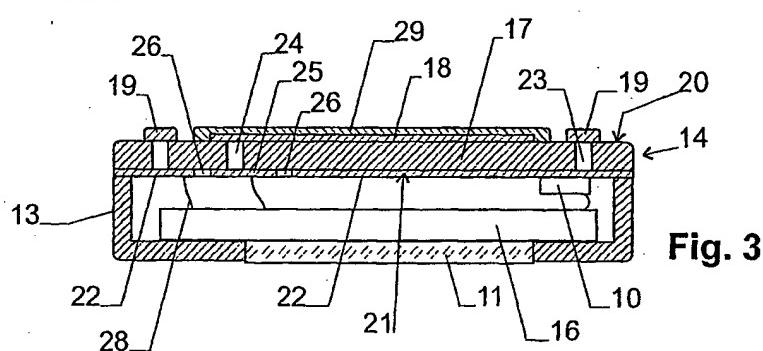
Fig. 3
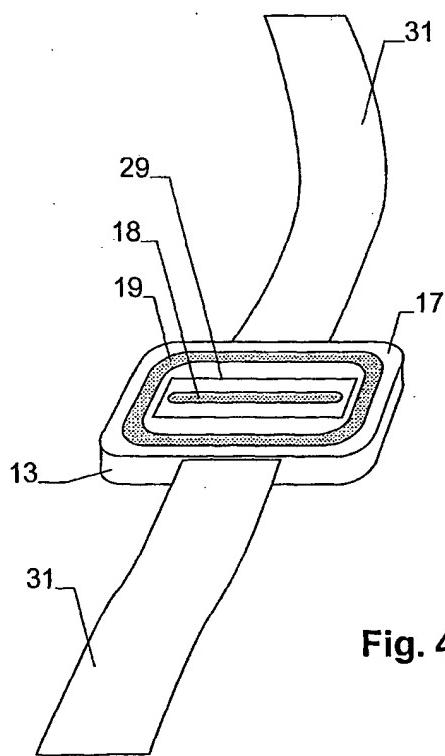
Fig. 4
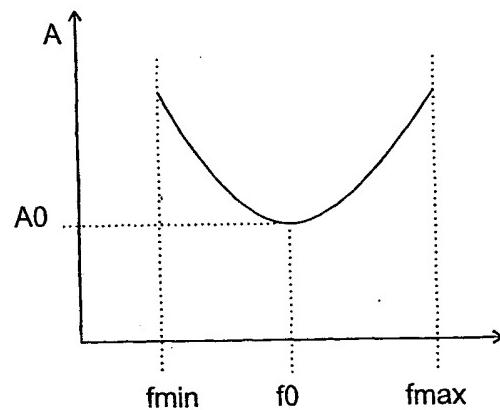
Fig. 5
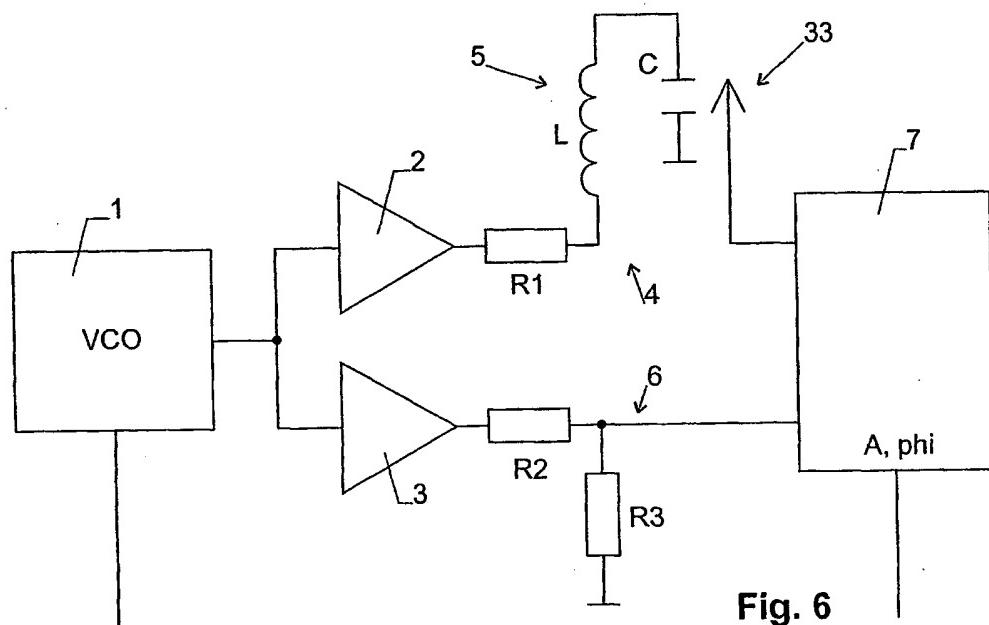
Fig. 6
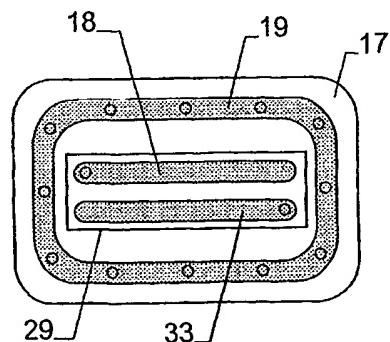
Fig. 7
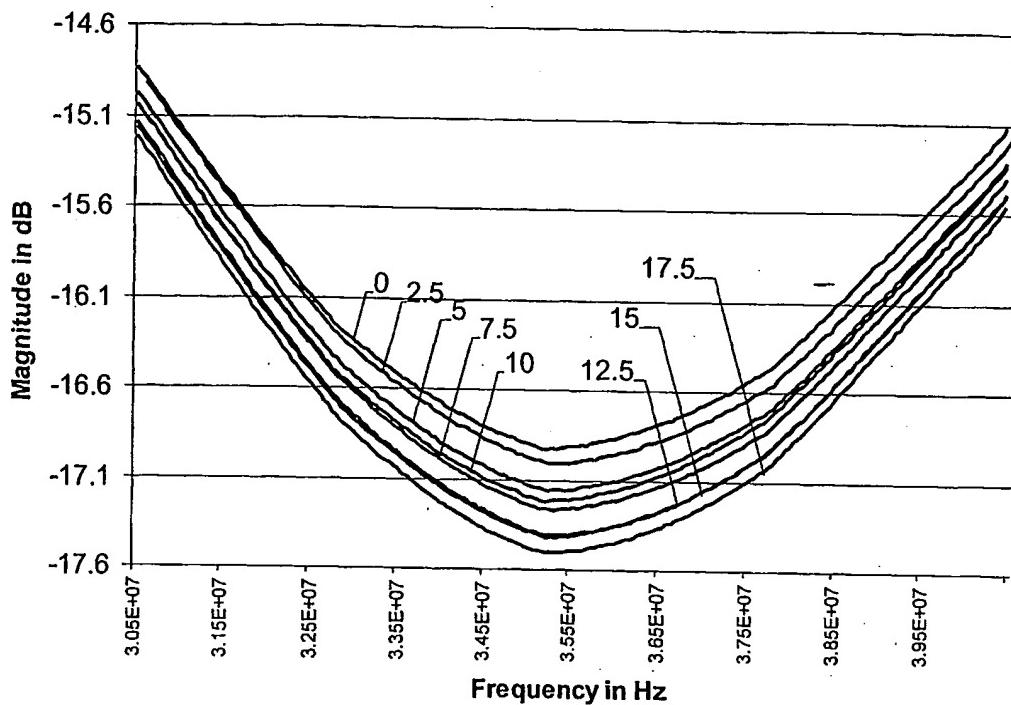
Fig. 8
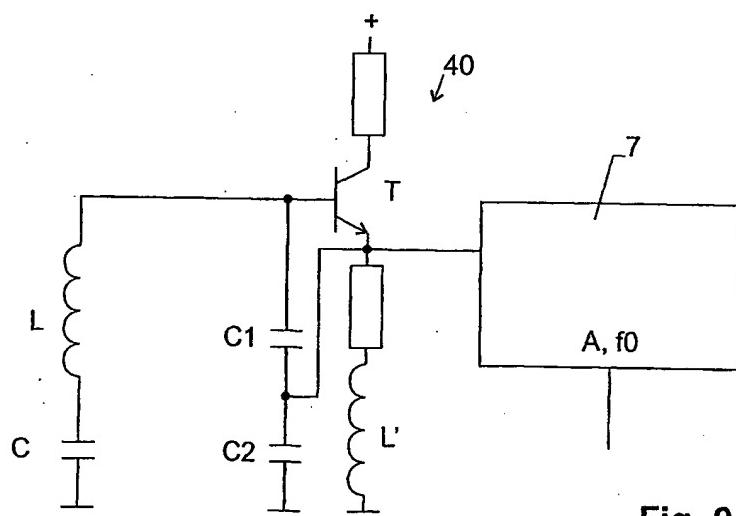
Fig. 9

INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7   A61B5/00   A61B5/05   G01N33/487   G01N22/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7   A61B   G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 792 668 A (DEAMER DAVID W ET AL) 11 August 1998 (1998-08-11) cited in the application abstract	16
A	WO 00 43759 A (LUCAS JAMES ;UNIV LIVERPOOL (GB); AL SHAMMAA AHMED (GB)) 27 July 2000 (2000-07-27) page 5 page 18; figure 17	16
A	EP 0 298 441 A (MED & TECH HANDELS GMBH) 11 January 1989 (1989-01-11) abstract; figure 1	16
A	EP 0 309 085 A (FISHER SCIENTIFIC CO) 29 March 1989 (1989-03-29) abstract	16

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[X] Further documents are listed in the continuation of box C.   [X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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Date of the actual completion of the international search	Date of mailing of the international search report
14 November 2001	21/11/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Jonsson, P.O.

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tional Application No

PCI/IB 01/00334

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 509 531 A (WARD JOHN W) 9 April 1985 (1985-04-09) abstract; figures 1-3 ---	
A	WO 85 04481 A (HEALTH LAB SERVICE BOARD) 10 October 1985 (1985-10-10) abstract -----	

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 5792668	A	11-08-1998	US	5508203 A	16-04-1996
			AU	731409 B2	29-03-2001
			AU	2974897 A	07-11-1997
			CA	2251919 A1	23-10-1997
			WO	9739341 A1	23-10-1997
			AU	676082 B2	27-02-1997
			AU	7520294 A	28-02-1995
			EP	0714259 A1	05-06-1996
			WO	9504496 A1	16-02-1995
WO 0043759	A	27-07-2000	AU	2115700 A	07-08-2000
			EP	1144985 A1	17-10-2001
			WO	0043759 A1	27-07-2000
			NO	20013603 A	13-09-2001
EP 0298441	A	11-01-1989	BR	8803351 A	17-01-1989
			EP	0298441 A2	11-01-1989
			ES	2048172 T3	16-03-1994
			AT	99148 T	15-01-1994
EP 0309085	A	29-03-1989	US	4751476 A	14-06-1988
			AU	1911388 A	23-03-1989
			EP	0309085 A2	29-03-1989
			JP	1132985 A	25-05-1989
US 4509531	A	09-04-1985	NONE		
WO 8504481	A	10-10-1985	AT	46219 T	15-09-1989
			AU	4213585 A	01-11-1985
			BR	8506431 A	15-04-1986
			CA	1239442 A1	19-07-1988
			DE	3572864 D1	12-10-1989
			DK	559785 A	03-12-1985
			EP	0176544 A1	09-04-1986
			WO	8504481 A1	10-10-1985
			HU	39015 A2	28-07-1986
			HU	200842 B	28-08-1990
			JP	5023624 B	05-04-1993
			JP	61501728 T	14-08-1986
			NO	854844 A	02-12-1985
			NO	164505 B	02-07-1990
			US	4876504 A	24-10-1989
			US	4810963 A	07-03-1989
			ZA	8502504 A	27-11-1985